Guidance for Industry

Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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CMC

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance provides the pharmaceutical industry with the Center for Drug Evaluation and Research's (CDER's) current thinking on the potential human health risks associated with exposure to dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). In particular, the draft guidance recommends that the pharmaceutical industry avoid the use of these two specific phthalates as excipients in CDER-regulated drug and biologic products, including prescription and nonprescription products.

The recommendations in this guidance do not address the use of DBP or DEHP in other types of FDA-regulated products or exposure to DBP or DEHP due to the presence of any of these compounds as an impurity—including as a result of leaching from packaging materials.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Phthalate esters (phthalates) are synthetic chemicals with a broad spectrum of uses. Phthalates are found in certain pharmaceutical formulations, primarily as a plasticizer in enteric-coatings of solid oral drug products to maintain flexibility, but they also may be used for different functions in other dosage forms. Phthalates also are found in other products for uses such as softeners of plastics, solvents in perfumes, and additives to nail polish, as well as in lubricants and insect repellents.

[1] This guidance has been prepared by the Office of Pharmaceutical Science, Office of New Drugs, Office of Compliance, and Office of Regulatory Policy in the Center for Drug Evaluation and Research at the Food and Drug Administration.

Phthalates have been studied extensively in animals, and some phthalates have demonstrated no appreciable toxicity. Certain phthalates, however, have been shown to be developmental and reproductive toxicants in laboratory animals. These phthalates are endocrine-disrupting chemicals in animals and may interfere with the production, secretion, transportation, metabolism, receptor binding, mediation of effects, and excretion of natural hormones that regulate developmental processes and support endocrine homeostasis in the organism. These same phthalates are suspected of being endocrine-disrupting in humans, and effects would depend on the systemic exposure (Jurewicz and Hanke 2011).

Data from the National Health and Nutrition Examination Survey (NHANES) indicate widespread exposure of the general population to phthalates (CDC 2009). Humans are exposed to phthalates by multiple routes, including inhalation, ingestion, and to a lesser degree absorption through the skin. Several observational human studies have reported an association between exposure to certain phthalates and adverse developmental and reproductive effects. The ubiquitous presence of phthalates in the environment and the potential consequences of human exposure to phthalates have raised concerns, particularly in vulnerable populations such as pregnant women and infants.

A number of regulatory authorities have begun taking steps to more closely regulate certain phthalates. For example:

- Congress has prohibited the use of DBP, DEHP, and another phthalate—butyl benzyl phthalate (BBP)—in children's toys at concentrations higher than 0.1 percent (Consumer Product Safety Improvement Act 2008).

- The European Commission identified DBP, DEHP, and BBP as reproductive toxicants (Directive 2005/84/EC), and the European Union prohibits their use as ingredients in cosmetics (Directive 2005/90/EC).

- The Environmental Protection Agency (EPA) added certain phthalates, including DBP and DEHP, to the list of chemicals of concern under the Toxic Substances Control Act and included them in the Toxics Release Inventory list (EPA 2009).

- FDA's Center for Devices and Radiological Health issued recommendations regarding minimizing exposure to PVC devices containing DEHP and provided recommendations for high-risk procedures (CDRH "DEHP in Plastic Medical Devices").

Of the phthalates for which significant concern has been expressed because of their reproductive and developmental toxicity, only DBP and DEHP have been used in CDER-regulated drug or biologic products. The recommendations in this guidance apply only to DBP and DEHP.

III. DISCUSSION

Phthalates have been studied extensively in animals, and DBP and DEHP have been shown to be developmental and reproductive toxicants in laboratory animals. While the data in humans are less clear, epidemiological studies suggest that certain phthalates may affect reproductive and developmental outcomes. Other studies have confirmed the presence of DBP and DEHP in amniotic fluid, breast milk, urine, and serum.

A. NONCLINICAL STUDIES

Phthalates generally have low acute toxicity in animals. However, repeated exposure to certain phthalates, including DBP and DEHP, in animals has been associated with various adverse effects—notably the disruption of the development of the male reproductive system.

Dibutyl Phthalate (DBP)

Exposure to DBP has been shown to cause decreased sperm counts in male animals and reduced fertility in both female and male animals. Exposure in pregnant animals has resulted in fetal skeletal malformations and decreased anogenital distance in the male offspring. Adverse effects on the male reproductive system have been seen in several species, including rats, mice, and guinea pigs (EPA 2006; Lehman et al. 2004). Male rats exposed directly to DBP for short periods of time at different stages of development also have shown abnormalities in reproductive development/function, including testicular atrophy and decreased spermatocytes and spermatogonia (Gray and Gangolli 1986; Cater et al. 1977). Some of these studies have indicated that adverse effects on male reproductive function can be seen in rats following a relatively short period of exposure to DBP.

Other studies in rodents have suggested that DBP may impair fertility in exposed females (Lehman et al. 2004). Finally, high doses of DBP have been associated with developmental abnormalities in rats, including skeletal abnormalities such as fusion or absence of cervical vertebral arches and fetal malformations such as cleft palate (Ema, Amano, and Ogawa 1994; Ema et al. 1995; Ema et al. 1993). Based on the adverse effects in animals, the EPA-recommended oral Reference Dose (RfD)[2] for DBP is 0.1 mg/kg/day.

Di(2-ethylhexyl) Phthalate (DEHP)

Exposure to DEHP has shown similar adverse effects as DBP on the male reproductive system. In a multigeneration continuous breeding study, exposure of female rats to DEHP resulted in F1 and F2 nonbreeding adult males with small or absent reproductive organs (NTP-CERHR 2005). In another study, female rats administered DEHP from gestation day 6 through lactation day 21 had male pups with nipple retention and reduced anogenital distance at a dose of 405 mg/kg/day, and delayed preputial separation was seen at doses of 15 mg/kg/day and above (Andrade et al. 2006). Oral exposure to approximately 100-200 mg/kg/day of DEHP during gestation resulted in skeletal and cardiovascular malformations, neural tube defects, developmental delays, and intrauterine death of the offspring. Based on these adverse effects in animals, the EPA-recommended RfD for DEHP is 0.02 mg/kg/day.

B. CLINICAL STUDIES

There are limited data on the health effects of DBP and DEHP in humans. Several studies have sought to quantify human exposure to phthalates using measurements of phthalate ester metabolites in urine. Phthalates are metabolized and excreted quickly, so urinary levels of phthalate ester metabolites reflect recent exposure to the parent diester. The Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009) provides data on levels of

[2] The RfD is an estimate of a daily oral exposure to human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

individual phthalate metabolites in the urine of several thousand participants who took part in the NHANES during 2003-2004. Researchers found measurable levels of many phthalate metabolites in the general population, indicating widespread exposure in the U.S. population to phthalate esters, including DBP and DEHP.

Studies measuring phthalate ester metabolite levels in pregnant women, maternal and umbilical cord plasma, and amniotic fluid samples have suggested that exposure to phthalates can occur in utero (Silva et al. 2004; Huang et al. 2009). Available human lactation data also show breast milk is a potential source of exposure to phthalate esters, including DBP and DEHP (Main et al. 2006).

Phthalate ester metabolites have been used as biomarkers to estimate exposure-related effects of phthalate esters, but these studies are only able to indicate association, not causation. Several such observational studies have shown an association between exposure to certain phthalates and adverse reproductive outcomes and developmental effects similar to those found in animals. In one study, maternal urinary concentrations of certain phthalate ester metabolites, including monoethyl phthalate (MEP) and mono-n-butyl phthalate (MBP), were negatively related to anogenital distance in newborn boys (Swan et al. 2005). Other studies evaluating the effects of phthalate exposure on adult males found a dose-response relationship between MBP (Hauser et al. 2006) with one or more semen parameters, including low sperm concentrations and motility.

IV. RECOMMENDATIONS

Although the current available human data are limited, the Agency has determined that there is evidence that exposure to DBP and DEHP from pharmaceuticals presents a potential risk of developmental and reproductive toxicity. While it is recognized that drug products may carry inherent risks, DBP and DEHP are used as excipients, and safer alternatives are available. Therefore, the Agency recommends avoiding the use of DBP and DEHP as excipients in CDER-regulated drug and biologic products.

These recommendations apply to CDER-regulated drug and biologic products that are under development (i.e., investigational new drugs (INDs)), nonapplication products (e.g., over the counter (OTC) monograph products), and both marketed approved products and those currently under review for marketing consideration (i.e., new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs)).

There are alternatives to DBP and DEHP for use as excipients in CDER-regulated products. Manufacturers with products that contain DBP or DEHP should consider alternative excipients and determine if the alternative excipient they plan to use has been used in similar CDER-approved products and at what level. The Inactive Ingredients Database provides information on excipients present in FDA-approved drug products, and this information can be helpful in developing drug products.[3]

[3] As manufacturers reformulate their products, the listings for dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) will be removed from the Inactive Ingredients Database (www.accessdata.fda.gov/scripts/cder/iig/index.cfm).

For any currently marketed formulation that includes DBP or DEHP, the applicable Scale-up and Post-Approval Changes (SUPAC) guidances should be referenced to determine the level of change to the formulation and the information (e.g., bridging studies) that should be submitted to support the change. (See, for example, SUPAC guidances for industry on Modified Release Solid Oral Dosage Forms (SUPAC-MR, September 1997); Nonsterile Semisolid Dosage Forms (SUPAC-SS, May 1997); and Immediate Release Solid Oral Dosage Forms (SUPAC-IR, November 1995).) The scientific thinking provided in the appropriate guidances also can be used for those products currently under development that may include DBP or DEHP. While the Inactive Ingredient Database lists the levels of excipients used in approved products per dosage form, manufacturers should take into account the total daily exposure at the maximal use conditions and contact the appropriate CDER review division to determine what studies supporting the use of the alternative excipient may be required. Additional studies also may be required if a novel excipient is used.

Manufacturers of currently marketed products approved under an NDA or ANDA should refer to the guidance for industry, *Changes to an Approved NDA or ANDA*, for information on the reporting category associated with a change in excipient (FDA guidance for industry April 2004). Questions related to nonapplication drug products should be directed to the appropriate CDER review division.

If a manufacturer determines that an alternative to DBP or DEHP cannot be used, the manufacturer should provide justification for why DBP or DEHP should be used. Such justification should include data to support why a safer alternative cannot be substituted, as well as a risk/benefit analysis that demonstrates that the benefit for the intended population outweighs potential safety concerns. The CMC information should be provided in Module 2 and Module 3 of a common technical document (CTD) formatted application, while nonclinical studies supporting the use of these phthalates in an application for a marketed drug product should be provided in Module 4 of a common technical document (CTD) formatted application.

A product marketed under an OTC monograph is generally recognized as safe and effective (and not misbranded) if the product conforms to the monograph and contains only suitable inactive ingredients that are safe in the amounts administered.[4] The Agency generally does not consider DBP or DEHP safe or suitable as an inactive ingredient in OTC monograph products.

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